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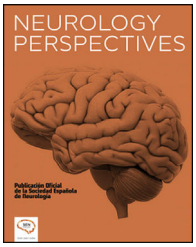

ORIGINAL ARTICLE

Characterisation and variables associated with mortality in a population with HIV and central nervous system opportunistic infections in a Colombian public hospital in Bogotá

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KEYWORDS
Human immunodeficiency virus (HIV);
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Mortality

Abstract
Introduction: HIV-associated mortality after a central nervous system opportunistic infection can reach up to 78%. In populations with limited economic resources, few studies have evaluated the clinical outcomes of these infections in patients with HIV.
Methods: We performed an observational analytical study using our hospital's database. Sociodemographic, clinical, and paraclinical data were gathered from patients with HIV-associated opportunistic neurological infections attended between January 2019 and January 2021. The aim of the study was to describe the in-hospital mortality rate and to establish associations with sociodemographic, clinical, and paraclinical variables.
Results: Seventy-five patients were included, with a mean age of 38.7 years. Fourteen (31.8%) were receiving antiretroviral therapy at the time of admission. The most frequent neurological infections were cerebral toxoplasmosis (37.3%, n = 28), meningeal cryptococcosis (20%, n = 15), and neurosyphilis (20%, n = 15). The in-hospital mortality rate was 25.3% (n = 19). The variables associated with increased mortality risk were diagnosis of meningeal cryptococcosis, admission to the ICU, and presence of fever. The variables associated with decreased mortality risk were CSF/blood glucose ratio > 0.5 and normal body mass index (18–25).
Conclusions: In a population of patients with HIV-associated opportunistic neurological infections, in-hospital mortality was 25.3%. The diagnosis of meningeal cryptococcosis, admission to the ICU, and the presence of fever are associated with higher mortality risk. To the contrary, CSF/blood glucose ratio > 0.5 and normal body mass index are associated with lower mortality risk.

Abbreviations: BUN, blood urea nitrogen; IL, interleukin; CSF, cerebrospinal fluid; CRP, C-reactive protein; AIDS, acquired immune deficiency syndrome; CNS, central nervous system; ART, antiretroviral therapy; ICU, intensive care unit; HIV, human immunodeficiency virus; BMI, body mass index

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PALABRAS CLAVE
Virus de inmunodeficiencia humana (VIH);
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Meningitis;
Terapia antirretroviral;
Mortalidad

Caracterización y factores asociados con mortalidad en población con VIH y neuroinfección oportunista en un hospital público en Bogotá, Colombia

Resumen
Introducción: La mortalidad asociada al VIH luego de una infección oportunista del SNC puede ser hasta del 78%. En poblaciones de bajos recursos económicos, existen pocos estudios que evalúen el desenlace clínico de estas infecciones en pacientes con VIH.
Metodología: Estudio observacional analítico usando la base de datos del hospital base de los investigadores. Se extrajeron datos sociodemográficos, clínicos y paraclínicos de los pacientes con neuroinfecciones oportunistas asociadas a VIH, entre enero del 2019 y enero del 2021. Se busca describir la mortalidad al final de la hospitalización y establecer asociaciones con las variables sociodemográficas, clínicas y paraclínicas.
Resultados: Se incluyeron 75 pacientes. La edad media fue 38.7 años. El 31.8% (n = 14) estaba recibiendo terapia anti-retroviral al momento del ingreso. Las neuroinfecciones más frecuentes fueron toxoplasmosis cerebral (37.3%, n = 28), criptococosis meníngea (20%, n = 15) y neurosífilis (20%, n = 15). La mortalidad al final de la hospitalización fue de 25.3% (n = 19). Las variables asociadas con aumento en la mortalidad fueron: diagnóstico de criptococosis meníngea, ingreso a UCI y presencia de fiebre. Las variables asociadas con disminución del riesgo de mortalidad fueron: relación de glucorraquia/glucemia mayor de 0.5 e IMC normal (18–25).
Conclusiones: En una población de pacientes con neuroinfección oportunista asociada a VIH, la mortalidad al final de la hospitalización fue de 25.3%. El diagnóstico de criptococosis meníngea, el ingreso a UCI y la presencia de fiebre, están asociadas con mayor riesgo de mortalidad. Por el contrario, una relación glucorraquia/glucemia mayor de 0.5 y un IMC normal están asociados con un menor riesgo de mortalidad.

Abreviaturas

BUN	nitrógeno ureico
IL	interleucina
LCR	líquido cefalorraquídeo
PCR	proteína C reactiva
SIDA	síndrome de inmunodeficiencia adquirida
SNC	sistema nervioso central
TAR	terapia antirretroviral
UCI	unidad de cuidado intensivo
VIH	virus de inmunodeficiencia humana
IMC	índice de masa corporal

Introduction

In 2020, approximately 38 million people worldwide had human immunodeficiency virus (HIV) infection, and circa 1.5 million people were infected de novo; a total of 680,000 HIV-related deaths were recorded that year.[1] In Colombia, the prevalence of HIV has increased over time, with 120,000 patients in 2010 and approximately 180,000 in 2020.[1] In 2021, 14,698 new cases were reported; 11.3% of these cases presented opportunistic infections, with 0.8% corresponding to cerebral toxoplasmosis.[1,2]

Central nervous system (CNS) involvement secondary to some opportunistic infection is estimated to constitute the initial symptom in 10%–20% of patients.[3] Furthermore, these infections define the AIDS stage and are associated with a high risk of mortality, with rates close to 50%.[4] The pathogenic agents vary according to geographical region. The most frequent infections in Latin America are cerebral toxoplasmosis, tuberculous meningitis, and cryptococcal meningitis, whereas in North America and Europe, the most frequent are progressive multifocal leukoencephalopathy, toxoplasma encephalitis, and cryptococcal meningitis.[5]

Since the introduction of antiretroviral therapy (ART), changes have been observed in the manifestation of neurological infections, with an increased age of onset and higher CD4 T lymphocyte counts at the time of diagnosis.[4] However, it has been reported that only 6.8% of patients with HIV-associated CNS opportunistic infections present virological suppression.[5] Furthermore, low CD4 T lymphocyte counts, high viral loads, and the lack of ART are associated with poorer prognosis, directly related to the higher risk of opportunistic infections.[6,7] Independently of the administration of ART, the factors influencing infection

with opportunistic pathogens include lack of knowledge of the stage of the disease, resistance to ART, poor treatment adherence, and the use of intravenous drugs that may interfere with medication pharmacokinetics.[6,7]

Some sociodemographic factors have been shown to increase the risk of HIV infection, while also influencing the course and outcomes of the disease. For instance, people with limited socioeconomic resources have been shown to present higher prevalence of HIV/AIDS and higher mortality rates.[8] The opportunistic infection associated with the highest mortality rate is cryptococcosis, followed by cerebral toxoplasmosis, disseminated tuberculosis, and *Pneumocystis jirovecii* pneumonia, regardless of the age of diagnosis with HIV infection, sex, ethnicity, CD4 T lymphocyte count, ART, transmission category, antibiotic prophylaxis, method of HIV infection, or development of other opportunistic infections.[7]

Despite the existence of ART, CNS infections have a significant impact on outcomes in patients with HIV infection, and therefore they remain a challenge for those physicians treating these infections. Few studies have been published in Latin American countries or populations with limited economic resources on the form of presentation and the variables associated with poorer prognosis. We conducted a study at a tertiary-level public hospital in Bogotá (Colombia) that serves a population of approximately 2.5 million people living in the south-west of the city. In 2017, 8.5%–21.2% of the population lived in poverty, with 3.4%–4.9% living in extreme poverty.[9] In our region, the rate of reported cases of HIV infection was 40.3–55.8/100000 population in 2019, and 41.4–56.4/100000 population in 2021; the mortality rate amounted to 2.4–4.4/100000 population in 2019 and 3.8–5.9/100000 population in 2021.[9]

It is important to determine the clinical and paraclinical characteristics of these patients to develop new strategies that may enable differential approaches with a positive impact on clinical outcomes. The aim of this study is to describe the clinical and paraclinical variables associated with in-hospital mortality among patients with a diagnosis of HIV-associated neurological infection attended at Hospital de Kennedy in Bogotá (Colombia), during the period between January 2019 and January 2021.

Methods

Study design and patient selection

We used the hospital database to conduct a retrospective study. We collected basic sociodemographic data, time from symptom onset to consultation, symptoms leading to consultation, the neurological infection diagnosed, HIV diagnostic status at the time of admission, use of ART, serum and cerebrospinal fluid (CSF) laboratory findings, head CT scan findings, intensive care unit (ICU) admission, duration of hospitalisation, concomitant infections outside the CNS, and outcome, defined as survival or death during hospitalisation. In this study, abnormal CT results were defined as presence of space-occupying lesions, with the remaining findings considered normal.

We selected these variables because they are usually described in CNS infections, and may have an impact on the prognosis and outcomes of these patients.[10,11] Some have been associated with a higher mortality rate specifically in populations with HIV infection, but have not been assessed in our population.[4,5,12]

Inclusion criteria were admission between January 2019 and January 2021, and diagnosis of HIV-associated CNS opportunistic infection. We excluded patients for whom information on outcomes was not available. The study was evaluated and approved by our hospital's ethics committee.

Statistical analysis

We performed a basic descriptive statistical analysis of the variables included. We calculated frequencies and percentages for categorical variables, and means and standard deviations for continuous variables. The minimum and maximum values were considered when relevant. The outcome was defined as the dichotomous dependent variable (death or survival). We performed a univariate analysis of the selected clinical and paraclinical variables. We used logistic regression to calculate odds ratios both for continuous and for categorical variables. We also calculated the confidence intervals and *P*-values. We established an alpha coefficient of 0.05 for statistical significance. All calculations were performed with version 16.1 of the Stata software.

Results

We included a total of 75 individuals. Mean age was 38.7 years, and the majority were men (Table 1). Of the total sample, 6 belonged to a special population: 5 intravenous drug users and one rough sleeper. The most frequent diagnosis was toxoplasmosis, in 37% of patients, followed by neurosyphilis and cryptococcosis, in 20% each, opportunistic neurological infection in 13%, and meningeal tuberculosis in 9%. The other infections were bacterial meningitis (3 patients), fungal infection other than with *Cryptococcus* (2 patients), herpes encephalitis (1 patient), coinfection with cryptococcosis and meningeal tuberculosis (1 patient), coinfection with neurosyphilis and cytomegalovirus (1 patient), coinfection with toxoplasmosis and cryptococcosis (1 patient), and neurological infection of undetermined cause in 1 patient. The most frequent symptom at admission was headache, in 64% of cases, followed by fever in 40% and altered level of consciousness in 24% (Table 1). HIV infection had been diagnosed previously in 58.7% of patients, with only 31% receiving ART. Twenty-five percent were admitted to the ICU. Mean hospital stay was 28.4 days, and 25% of patients died during admission.

Of the 69 patients for whom data were available on CD4 T lymphocyte count, 76% presented levels below 200 cells/mm^3, with a mean count of 102 cells/mm^3. Fifty-eight (77%) patients underwent a lumbar puncture. Mean CSF opening pressure was 22.8 cm H_2O (normal range: 6–25); 55% presented normal glucose levels (>50 mg/dL), although approximately 61% showed a CSF/blood glucose ratio < 0.5. Sixty-four percent presented elevated CSF protein level (>45 mg/dL), with 38% displaying pleocytosis. Table 2 shows the blood, CSF, and cranial CT scan findings.

Table 1 Patient clinical and demographic characteristics.

Mean age, years (SD)		38.7 (12.5)
Sex, n (%)	Men	55 (73.3)
	Women	20 (26.7)
BMI, mean (SD) (normal range: 18–25 kg/m^2)		20.9 (3.8)
Known diagnosis of HIV infection	Yes	44 (58.7)
	No	31 (41.3)
ART (n = 44), n (%)	Yes	14 (31.8)
	No	30 (68.2)
Mean time since diagnosis of HIV infection, months (SD)		43 (112)
Mean time between symptom onset and consultation, days (SD)		20.5 (48.9)
Signs and symptoms at admission, n (%)	Fever	30 (40)
	Headache	48 (64)
	Altered level of consciousness	18 (24)
	Meningeal signs	15 (20)
	Epileptic seizure	18 (24)
Diagnosis, n (%)	Cerebral toxoplasmosis	28 (37.3)
	Meningeal cryptococcosis	15 (20)
	Meningeal tuberculosis	7 (9.3%)
	Neurosyphilis	15 (20)
	Other infection	10 (13.3)
Mean hospital stay, days (SD)	28.4 (17.3)	
ICU admission, n (%)	19 (25.3)	
Death, n (%)	19 (25.3)	

The variables associated with in-hospital mortality were fever at admission (P = .02), diagnosis of meningeal cryptococcosis (P = .02), and admission to the ICU (P = .004). We also observed that mortality risk increased by 1.28 times for every 1000 neutrophils in the blood count (P = .015) and by 1.14 times for every increment of mg/dL in blood urea nitrogen (BUN) (P = .003) (Table 3).

Additionally, we observed a decrease in mortality risk associated with each 10 cell/μL increment in the CD4 T lymphocyte count (P = .02), with CSF/blood glucose ratios above 0.5 (P = .07), and with BMI within normal ranges (18–25) (P = .03) (Table 3).

Discussion

In a vulnerable population with limited economic resources, we found that the most frequent opportunistic infections in patients with HIV infection were cerebral toxoplasmosis, meningeal cryptococcosis, neurosyphilis, and meningeal tuberculosis. In this group of patients, in-hospital mortality amounted to 25.3%. We have found no other studies assessing the overall mortality rate in patients with HIV-associated CNS opportunistic infections. Published studies have focused on the mortality associated with certain opportunistic neurological infections, such as cryptococcosis and meningeal tuberculosis, and describe mortality rates ranging from 13% to 44%.[8,12,13]

In our study, the variables associated with higher mortality rates were fever, meningeal cryptococcosis infection, ICU admission, increased neutrophil count, and increased BUN. The variables associated with a lower risk of mortality were CSF/blood glucose ratio > 0.5, high CD4 T lymphocyte counts, and normal body mass index.

Fever in the context of immunosuppression or neutropenia has been described as a manifestation of severe infection, and increases the mortality risk by up to 50% if the infection is not adequately treated within the first 48 h.[14] Presence of fever is reported to be correlated with a lower mortality in patients with septic shock.[15,16] However, some studies have found that in patients with cerebral pathology (head trauma, subarachnoid haemorrhage, or stroke), hyperthermia may exacerbate brain tissue lesions due to an increased neuronal metabolic rate, decreased cerebral blood flow, exacerbation of oedema, and blood–brain barrier dysfunction, which leads to greater impairment and higher mortality.[15,17,18] This may support our findings, which describe a higher mortality rate in patients with associated fever.

Meningeal cryptococcosis is the main cause of death in patients with HIV-associated CNS opportunistic infections.[19,20] This is consistent with our findings, which revealed 5.25 times greater mortality risk than that calculated for the remaining opportunistic infections. Furthermore, a systematic review reported a mortality rate of up to 78% in patients with HIV-associated meningeal cryptococcosis, compared to 42% among patients with the same opportunistic neurological infection but without diagnosis of HIV infection.[17] Although the generalised use of ART and azoles has led to a decrease in prevalence, the mortality rate remains high, as many patients present delayed diagnosis or have no means of accessing optimal long-term therapy, especially in low-income areas such as Sub-Saharan Africa, where this infection is estimated to cause 625,000 deaths annually.[18] A 5-year follow-up study in that region estimated a mortality rate of 20%–25%, with a 6-month survival rate greater than 88%.[21]

Table 2 Paraclinical symptoms.

			n (%)	Mean (SD)
Viral load, copies/mL				4,794,891 (1495526)
CD4 T lymphocyte count, cells/mm^3 (n = 69)				102.6 (123.4)
	<200		57 (76)	
Blood chemistry study	Creatinine (mg/dL)			1.03 (1.62)
	BUN, mg/dL			14.01 (6.8)
	Sodium, mmol/L			137.3 (5.02)
Lumbar puncture			58 (77.3)	
	Opening pressure, cm H_2O (normal range: 6–25 cm H_2O)	<25	41 (71.9)	
		>25	16 (28.1)	
	CSF glucose level, mg/dL	<45	26 (44.8)	
		>45	32 (55.2)	
	CSF protein level	<45	21 (36.2)	
		>45	37 (63.8)	
	CSF/blood glucose ratio	<0.5	34 (61.3)	
		>0.5	21 (38.2)	
	Leukocytes, cells/mm^3	<5	36 (62.1)	
		>5	22 (37.9)	
Complete blood count	Leukocytes, cells/mm^3	<4000	12 (16)	
		4000–11,000	54 (72)	
		>11,000	9 (12)	
	Lymphocytes, cells/mm^3	<800	12 (16)	
		800–5000	52 (69.3)	
		>5000	11 (14.7)	
	Neutrophils, cells/mm^3	<1500	11 (14.7)	
		1500–8000	57 (76)	
		>8000	7 (9.3)	
	Platelets	<150,000	9 (12)	
		150,000–400,000	59 (78.7)	
		>400,000	7 (9.3)	
CRP	>0.5		50 (79.4)	
Simple head CT scan	Abnormal		44 (60.3)	

Regarding ICU admissions and mortality in patients with HIV infection, variable rates have been described, which have decreased since the implementation of ART; however, they remain high, and vary according to the region studied, fluctuating between 20%–30% in Europe and North America, and 37%–68% in such countries as Chile, Brazil, Mexico, China, and Australia. This seems to be related to a poorer immunovirological status in patients admitted to the ICU.[22,23] This is in line with our results, which showed that admission to the ICU was associated with 5.8 times greater risk of mortality.

Table 3 Variables associated with decreased and increased mortality risk in patients with HIV-associated opportunistic neurological infection.

	OR	95% CI	*P*
Decreased mortality risk			
BMI (18–25)	0.24	0.067–0.87	0.03
CD4 T lymphocyte count (×10)	0.85	0.74–0.97	0.020
CSF/blood glucose ratio (>0.5)	0.07	0.001–0.58	0.004
Increased mortality risk			
Meningeal cryptococcosis	5.25	1.29–21.35	0.02
Fever	3.61	1.07–12.63	0.02
ICU admission (yes/no)	5.8	1.57–21.27	0.004
Neutrophils (×1000)	1.28	1.04–1.56	0.015
Blood urea nitrogen	1.14	1.04–1.26	0.003

With regard to the increase in BUN, altered renal function has been described in the initial stages of HIV infection[24] and in the presence of such opportunistic infections as tuberculosis and histoplasmosis[25,26]; however, BUN has not been studied as a factor associated with mortality, and further studies are needed in this regard. Regarding neutrophil counts, neutropenia frequently manifests in HIV infection, due to a range of mechanisms.[14] Its impact has been mainly studied in cryptococcosis, and neutrophils are considered part of the host immune response, playing a regulatory role in the balance of Th1/Th2 responses. Its effect on the outcomes of the infection may be beneficial or detrimental depending on the type of pathogen involved.[27] In the specific case of cryptococcosis, studies with animal models report that an increase in neutrophil count is associated with a more severe Th1 response that may lead to greater tissue damage and poorer clinical outcomes. On the other hand, in the context of neutropenia, a greater Th2 response is generated, with increased production of IL-4 and IL-10, which may help reduce the tissue damage as a result of the

inflammatory process; together with a decreased Th1 response, this would explain why neutropenic animal models present better survival.[28] This is consistent with our own results and may explain why the increase in the total neutrophil count was associated with an increased mortality risk.

With respect to CD4 T lymphocyte count, higher levels have been associated with a lower mortality rate,[10] especially with counts higher than 200 cells/mm^3.[29] This is in line with our results, which showed a decrease in mortality risk with every increment of 10 cells/mm^3. Viral load was also identified as a direct marker of HIV infection, with an increase of 10^4 copies/mL being associated with 1.02 times greater mortality risk.

Low CSF glucose levels have been described as a predictor of mortality in the first year after neurological infection in HIV-positive patients.[30] This is consistent with our results, which showed lower mortality risk in patients with a normal CSF/blood glucose ratio (>0.5). Furthermore, an association between low body weight and mortality has been described in patients with HIV infection, and it is reported that mortality risk decreases as body weight increases.[31] In our study, we observed that a normal BMI was associated with lower mortality rate.

In our population, a high percentage of patients (68.2%) with a known diagnosis of HIV infection were not receiving ART. Adherence to ART is an essential factor in predicting the clinical outcomes and mortality rate associated with HIV infection.[32,33]

Some studies have found that lack of adherence to ART is a risk factor for viral changes (transient increases of HIV RNA in plasma), virological failure, drug resistance, and increased mortality.[31] Additionally, since the 1990s, ART programmes have been established in Latin America, the Caribbean, South-East Asia, and Sub-Saharan Africa; however, treatment access still represents a challenge, especially in developing countries.[34,35] In Latin America and the Caribbean, only 42% of individuals are estimated to receive treatment.[34] Despite this, we did not find a statistically significant association between treatment adherence and mortality; however, our methodology was not designed to predict causal associations, and more specific studies are therefore needed to establish more precise associations in our population.

Limitations

The main limitations of our study are related to the retrospective data collection. The lack of data is clear for some variables. Additionally, our sample was collected from the database of a single hospital, with patients being selected by convenience sampling, which may have led to a selection bias. The specific conditions of the population attended at our hospital are not representative of the general population; therefore, the results are only applicable to similar populations to that described. There may be an information bias related to the patient interview performed at admission as, despite being conducted by specialist physicians and residents with sufficient training, the interview is not standardised, and questions regarding symptoms may not have been the same for all the reported symptoms. Lastly, there is a possible Neyman bias regarding patients with neurosyphilis, which is relatively frequently diagnosed after active search in patients with HIV infection and no neurological symptoms but with serological diagnosis of late latent syphilis

Conclusions

In our public hospital, which attends a population with limited socioeconomic resources, toxoplasmosis is the most frequently diagnosed CNS opportunistic infection in patients with HIV infection. However, meningeal cryptococcosis is the infection associated with the greatest increase in mortality risk. Approximately one in every 4 patients dies, and mortality is higher in those presenting fever at admission, requiring ICU admission, with higher total blood neutrophil count, and with increased BUN concentration. On the contrary, mortality is lower in those with normal BMI, with higher CD4 T lymphocyte count, and without low CSF glucose level. These findings help us to define the parameters to be closely monitored in patients with HIV infection and opportunistic neurological infections. The methodology of this study does not allow us to establish causal associations, but our results may be useful in the design of prevention policies to decrease mortality among these patients. Further prospective studies are needed to confirm these findings.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurop.2023.100127.

References

1. Joint United Nations Programme on HIV/AIDS. UNAIDS Data 2021. Programme on HIV/AIDS; 2020;1–436. Disponible en: https://www.unaids.org/sites/default/files/media_asset/JC3032_AIDS_Data_book_2021_En.pdf. [consultada el 14 de Noviembre del 2022].
2. Colombia. Instituto Nacional de Salud. Boletín Epidemiológico Semanal -BES-, Colombia. Semana Epidemiológica. 2021;47 21 al 27 de noviembre de. Disponible en: https://www.ins.gov.co/buscador-eventos/BoletinEpidemiologico/Forms/AllItems.aspx. [consultada el 14 de Noviembre del 2022].

3. Sacktor N, Lyles RH, Skolasky R, Kleeberger C, Selnes OA, Miller EN, et al. Multicenter AIDS Cohort Study. HIV-associated neurologic disease incidence changes: Multicenter AIDS Cohort Study, 1990-1998. Neurology. 2001 Jan 23;56(2):257–60. https://doi.org/10.1212/wnl.56.2.257.
4. Luma HN, Tchaleu BC, Temfack E, Doualla MS, Ndenga DP, Mapoure YN, et al. HIV-associated central nervous system disease in patients admitted at the douala general hospital between 2004 and 2009: a retrospective study. AIDS Res Treat. 2013:1–6. https://doi.org/10.1155/2013/709810.
5. Matinella A, Lanzafame M, Bonometti MA, Gajofatto A, Concia E, Vento S, et al. Neurological complications of HIV infection in pre-HAART and HAART era: a retrospective study. J Neurol. 2015 May;262(5):1317–27. https://doi.org/10.1007/s00415-015-7713-8.
6. Bowen LN, Smith B, Reich D, Quezado M, Nath A. HIV-associated opportunistic CNS infections: pathophysiology, diagnosis and treatment. Nat Rev Neurol. 2016 Oct 27;12(11):662–74. https://doi.org/10.1038/nrneurol.2016.149.
7. Djawe K, Buchacz K, Hsu L, Chen MJ, Selik RM, Rose C, et al. Mortality risk after AIDS-defining opportunistic illness among HIV-infected persons-San Francisco, 1981-2012. J Infect Dis. 2015 Nov 1;212(9):1366–75. https://doi.org/10.1093/infdis/jiv235.
8. El Fane M, Badaoui L, Ouladlahsen A, Sodqi M, Marih L, Chakib A, et al. La cryptococcose au cours de l'infection à VIH [Cryptococcosis during HIV infection]. J Mycol Med. 2015 Dec;25(4):257–62. French: https://doi.org/10.1016/j.mycmed.2015.09.008.
9. Secretaría Distrital de Salud. Observatorio de Salud de Bogotá-SaluData. Disponible en: https://saludata.saludcapital.gov.co/osb/; 2022. [consultada el 24 de Noviembre del 2022].
10. Buchholz G, Koedel U, Pfister HW, Kastenbauer S, Klein M. Dramatic reduction of mortality in pneumococcal meningitis. Crit Care. 2016 Oct 2;20(1):312. https://doi.org/10.1186/s13054-016-1498-8.
11. de Fátima Magalhães Acioly Mendizabal M, Bezerra PC, Guedes DL, Cabral DB, de Barros Miranda-Filho D. Prognostic indicators in bacterial meningitis: a case-control study. Braz J Infect Dis. 2013 Sep-Oct;17(5):538–44. https://doi.org/10.1016/j.bjid.2013.01.016.
12. Brizendine KD, Baddley JW, Pappas PG. Predictors of mortality and differences in clinical features among patients with Cryptococcosis according to immune status. PLoS One. 2013;8(3), e60431. https://doi.org/10.1371/journal.pone.0060431.
13. Pormohammad A, Nasiri MJ, Riahi SM, Fallah F. Human immunodeficiency virus in patients with tuberculous meningitis: systematic review and meta-analysis. Tropical Med Int Health. 2018 Jun;23(6):589–95. https://doi.org/10.1111/tmi.13059.
14. White L, Ybarra M. Neutropenic fever. Hematol Oncol Clin North Am. 2017 Dec;31(6):981–93. https://doi.org/10.1016/j.hoc.2017.08.004.
15. Kiekkas P, Aretha D, Bakalis N, Karpouhtsi I, Marneras C, Baltopoulos GI. Fever effects and treatment in critical care: literature review. Aust Crit Care. 2013 Aug;26(3):130–5. https://doi.org/10.1016/j.aucc.2012.10.004.
16. Ryan M, Levy MM. Clinical review: fever in intensive care unit patients. Crit Care. 2003 Jun;7(3):221–5. https://doi.org/10.1186/cc1879.
17. Aiyagari V, Diringer MN. Fever control and its impact on outcomes: what is the evidence? J Neurol Sci. 2007 Oct 15;261(1–2):39–46. https://doi.org/10.1016/j.jns.2007.04.030.
18. Sacho RH, Childs C. The significance of altered temperature after traumatic brain injury: an analysis of investigations in experimental and human studies: part 2. Br J Neurosurg. 2008 Aug;22(4):497–507. https://doi.org/10.1080/02688690802245558.
19. Pasquier E, Kunda J, De Beaudrap P, Loyse A, Temfack E, Molloy SF, et al. Long-term mortality and disability in cryptococcal meningitis: a systematic literature review. Clin Infect Dis. 2018 Mar 19;66(7):1122–32. https://doi.org/10.1093/cid/cix870.
20. Spec A, Powderly WG. Cryptococcal meningitis in AIDS. Handb Clin Neurol. 2018;152:139–50. https://doi.org/10.1016/B978-0-444-63849-6.00011-6.
21. Butler EK, Boulware DR, Bohjanen PR, Meya DB. Long term 5-year survival of persons with cryptococcal meningitis or asymptomatic subclinical antigenemia in Uganda. PLoS One. 2012;7(12), e51291. https://doi.org/10.1371/journal.pone.0051291.
22. Vidal-Cortés P, Álvarez-Rocha LA, Fernández-Ugidos P, Pérez-Veloso MA, Suárez-Paul IM, Virgós-Pedreira A, et al. Epidemiology and outcome of HIV-infected patients admitted to the ICU in the current highly active antiretroviral therapy era. Med Intensiva (Engl Ed). 2020 Jun-Jul;44(5):283–93. https://doi.org/10.1016/j.medin.2019.02.012.
23. Verdugo F, Pinto F, Charpentier P, Von Mühlenbrock C, Soto A, Dabanch J, et al. Pacientes con infección por VIH/SIDA en una Unidad de Pacientes Críticos: La experiencia de un hospital general en un país en desarrollo [HIV/AIDS patients in a Critical Care Unit: The experience of a general hospital in a developing country]. Rev Chil Infectol. 2015 Jun;32(3):294–303. https://doi.org/10.4067/S0716-10182015000400007.
24. Olusola BA, Kabelitz D, Olaleye DO, Odaibo GN. Early HIV infection is associated with reduced proportions of gamma delta T subsets as well as high creatinine and urea levels. Scand J Immunol. 2020 May;91(5). https://doi.org/10.1111/sji.12868 e12868.
25. Alvarez-Uria G, Midde M, Naik PK. Mortality in HIV-infected patients with tuberculosis treated with streptomycin and a two-week intensified regimen: data from an HIV cohort study using inverse probability of treatment weighting. PeerJ. 2016 May 17(4), e2053 https://doi.org/10.7717/peerj.2053.
26. Boigues BCS, Paniago AMM, Lima GME, Nunes MO, Uehara SNO. Clinical outcomes and risk factors for death from disseminated histoplasmosis in patients with AIDS who visited a high-complexity hospital in Campo Grande, MS. Brazil Rev Soc Bras Med Trop. 2018 Mar-Apr;51(2):155–61. https://doi.org/10.1590/0037-8682-0369-2017.
27. Musubire AK, Meya DB, Rhein J, Meintjes G, Bohjanen PR, Nuwagira E, et al. Blood neutrophil counts in HIV-infected patients with cryptococcal meningitis: Association with mortality. PLoS One. 2018 Dec 31;13(12), e0209337. https://doi.org/10.1371/journal.pone.0209337.
28. Mednick AJ, Feldmesser M, Rivera J, Casadevall A. Neutropenia alters lung cytokine production in mice and reduces their susceptibility to pulmonary cryptococcosis. Eur J Immunol. 2003 Jun;33(6):1744–53. https://doi.org/10.1002/eji.200323626.
29. Berhe T, Melkamu Y, Amare A. The pattern and predictors of mortality of HIV/AIDS patients with neurologic manifestation in Ethiopia: a retrospective study. AIDS Res Ther. 2012 Apr 10(9):11 https://doi.org/10.1186/1742-6405-9-11.
30. Tenforde MW, Mokomane M, Leeme TB, Tlhako N, Tsholo K, Chebani T, et al. Mortality in adult patients with culture-positive and culture-negative meningitis in the Botswana national meningitis survey: a prevalent cohort study. Lancet Infect Dis. 2019 Jul;19(7):740–9. https://doi.org/10.1016/S1473-3099(19)30066-0.
31. Sharma A, Hoover DR, Shi Q, Gustafson D, Plankey MW, Hershow RC, et al. Relationship between body mass index and mortality in HIV-infected HAART users in the women's interagency HIV study. PLoS One. 2015 Dec 23;10(12), e0143740. https://doi.org/10.1371/journal.pone.0143740.

32. Taiwo B. Adherence to antiretroviral therapy: the more you look, the more you see. Curr Opin HIV AIDS. 2009 Nov;4(6):488–92. https://doi.org/10.1097/COH.0b013e3283311058.
33. Djawe K, Buchacz K, Hsu L, Chen MJ, Selik RM, Rose C, et al. Mortality risk after AIDS-defining opportunistic illness among HIV-infected persons—San Francisco, 1981–2012. J Infect Dis. 2015 Nov 1;212(9):1366–75. https://doi.org/10.1093/infdis/jiv235.
34. Beaulière A, Le Maux A, Trehin C, Perez F. Access to antiretroviral treatment in developing countries: which financing strategies are possible? Rev Epidemiol Sante Publique. 2010 Jun;58 (3):171–9. https://doi.org/10.1016/j.respe.2010.03.002.
35. WHO/UNAIDS/Unicef. Toward universal access: scaling up priority HIV/AIDS interventions in the health sector: progress report.Geneva: World Health Organization; 2009. Disponible en: http://www.who.int/hiv/pub/. [consultada el 14 de Noviembre del 2022].